ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 10, 2025

Online - 2455-3891
Print - 0974-2441

Review Article

ADVANCES IN ANTIFUNGAL THERAPY FOR ONCHOMYCOSIS: A FOCUS ON EMERGING AGENTS AND TECHNOLOGIES

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Received: 03 June 2025, Revised and Accepted: 06 August 2025

ABSTRACT

Onychomycosis, a persistent fungal infection of the nails, is a therapeutic challenge because of its high recurrence, poor drug penetration, and resistance developed by the fungus to common antifungals (AFs). "The available therapies, such as oral azoles and topicals, can have limited efficacy, lengthy duration of treatment, or potential side effects," they added. This has created a demand for new and better AF tactics. Novel AFs whose development has been fueled by recent advances in our understanding about fungal biology are the newer (most are second-line for invasive mycoses) broad-spectrum systemic agents with superior pharmacokinetic profiles and lower toxicities, as seen with improved azole derivatives and allylamines. Systemic AF therapy nanotechnology-mediated drug delivery systems, such as nanoparticle encapsulated AFs and liposomal formulations, have promising potential for increased drug penetration and therapeutic efficacy. In resistant cases, non-pharmacological measures such as photodynamic therapy and lasers are increasingly being considered. In addition, emerging approaches, such as microbiome-targeted interventions and RNA-based treatments, provide new methods for addressing fungal biofilms and recalcitrant infections. However, significant challenges exist in the translation of these novel therapies into clinical practice, and research efforts continue to be made toward refining modifications of treatment algorithms and enhancing patient efficacy. The present review summarizes the new therapeutic approaches to onychomycosis with a special emphasis on the mechanism, clinical efficacy, and future development. The convergence of innovative anti-fibrotic agents (AFs), nanotechnology, and novel therapeutic approaches holds promise for the development of more efficacious and tolerable treatments in the near future.

Keywords: Antifungal therapy, Onychomycosis, Next-generation antifungals, Fungal biofilms, Drug resistance, Photodynamic therapy, Nanotechnology.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i10.55391. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Onychomycosis, a chronic fungal infection of the nail, affects 10–12% of the global population and is among the most common nail disorders [1]. It is primarily caused by dermatophytes such as *Trichophyton rubrum* and *Trichophyton mentagrophytes*, though non-dermatophyte molds and yeasts such as *Candida* spp. can also be involved [2]. The infection typically begins as a small spot and progresses to thickened, brittle, and deformed nails, impairing activities such as walking and handling objects [3]. Although often viewed as a cosmetic issue, it can have serious consequences, particularly in diabetics and immunocompromised individuals, where it may lead to secondary bacterial infections, cellulitis, or chronic ulcers. Recurrence and slow nail growth make treatment challenging [4]. Oral antifungals (AF) such as terbinafine and itraconazole are standard treatments due to their nail bed penetration, but their use is limited by long treatment durations (up to 12 weeks), liver toxicity, and drug interactions, especially in elderly and hepatically compromised patients [5]. Topical agents such as ciclopirox and efinaconazole are safer but have limited penetration and require prolonged application with modest cure rates [6]. The thickened nail plate and formation of fungal biofilms act as physical and biological barriers, leading to drug resistance, recurrent infections, and treatment failure [7].

AF resistance is increasing, driven by mechanisms such as gene mutations, efflux pump activation, and metabolic changes in fungi [8]. These challenges highlight the urgent need for new AF strategies in dermatology. Due to limitations of current therapies, novel approaches are being investigated to enhance efficacy and reduce side effects [9]. New systemic AFs such as oteseconazole and fosravuconazole show promise with improved fungal selectivity, safety, and patient adherence [10]. In addition, innovative topical formulations, including benzoxaborole-based drugs and nanoparticles (NPs), aim to overcome nail penetration barriers and improve local drug retention [11]. Nanotechnology-based delivery systems such as liposomes, solid lipid NPs, and metallic NPs are being studied to enhance drug delivery and sustain AF action at the infection site [12]. Moreover, non-pharmacological therapies, including photodynamic therapy (PDT), laser therapy, and microbiome-based interventions, are emerging as promising alternatives, especially in resistant cases or when conventional treatments are limited [13].

This review discusses recent advances in onychomycosis management, covering novel AF agents, advanced drug delivery technologies, and innovative non-drug therapies [14]. By examining current clinical trials and experimental treatments, we aim to provide clinicians with an updated perspective on evolving therapeutic options and future directions in the management of onychomycosis [15].

STAGES OF ONYCHOMYCOSIS INFECTION

Onychomycosis is a common fungal infection of the nail apparatus that progresses in distinct clinical stages shown in Fig. 1, from mild discoloration to complete nail dystrophy. Understanding the natural history of the disease is critical for timely diagnosis, effective treatment, and prevention of complications [16].

Initial stage: Early infection

In the early phase, onychomycosis often presents with minimal clinical symptoms. The hallmark features include subtle discoloration – commonly white, yellow, or off-white – typically localized to the distal or lateral margins of the nail plate. Nail thickening is mild or absent, and structural integrity is usually maintained [17]. Dermatophytes, particularly *T. rubrum*, are the most common etiological agents at this stage [18]. Two frequent subtypes may be observed:

Distal lateral subungual onychomycosis

Begins at the hyponychium or lateral nail fold and spreads proximally [19].

Superficial white onychomycosis

Involves superficial patches of white discoloration on the nail plate surface [20].

Diagnosis at this stage can be challenging due to the subtle presentation, but early identification is crucial for effective management and prevention of disease progression [21].

Moderate stage: Established infection

As the infection advances, more pronounced clinical features emerge. These include increased nail discoloration (yellow, brown, or chalky white), thickening of the nail plate, and friability. Onycholysis – detachment of the nail plate from the nail bed – is often evident, along with subungual hyperkeratosis, which manifests as keratinous debris under the nail [22]. Pain is usually absent or mild, but cosmetic concerns are common. At this stage, more than 25% of the nail plate may be affected, and the infection may begin to spread to adjacent nails [23].

Advanced stage: Severe infection

The advanced stage is characterized by marked nail dystrophy, deformity, and discoloration. The nail plate becomes significantly thickened and deformed, with potential complete separation from the nail bed [24]. Patients frequently report pain, particularly when wearing shoes or during ambulation, in cases involving toenails. Foul odor and secondary bacterial infection may also occur [25]. This stage often leads to a substantial decline in nail function and esthetics, with social and psychological implications [26].

Chronic stage: Long-term untreated infection

In chronic cases – particularly when left untreated or inadequately treated – the infection can result in irreversible nail damage. Nails become severely dystrophic, discolored, and brittle, often involving multiple digits [27]. This stage may be complicated by secondary infections such as cellulitis, especially in immunocompromised or diabetic patients [28]. Chronic onychomycosis is associated with reduced quality of life and can serve as a reservoir for continued fungal transmission [29].

Special variants and considerations

Proximal subungual onychomycosis

A less common form that begins at the proximal nail fold and progresses distally. It is often seen in immunocompromised individuals, including those with human immunodeficiency virus/acquired immunodeficiency syndrome [30].

Candidal onychomycosis

Caused by *Candida* spp., it predominantly affects fingernails and may be associated with paronychia or chronic mucocutaneous candidiasis [31].

PATHOGENESIS AND DRUG RESISTANCE MECHANISMS

Onychomycosis is a long-lasting fungal infection that is mainly caused by dermatophytes, and among them, *T. rubrum* is the most common species, and *T. mentagrophytes* is the second most common one [32]. These fungi are adapted for growth on keratinized tissues, where they produce enzymes such as keratinases, proteases, and lipases to degrade the nail matrix and shaft structure, which facilitates their entry into deeper layers. Dermatophytes are the most frequent causative organisms, but NDMs, e.g.,: *Scopulariopsis brevicaulis*, *Aspergillus* species, and yeasts, such as *Candida albicans,* have been increasingly implicated, especially in immunocompromised or very wet feet. Variability in the fungal species also leads to differences in treatment outcomes since some fungi are naturally more resistant to routine AF drugs [33].

A major obstacle in managing onychomycosis is fungal biofilm formation, which promotes drug resistance. Biofilms are structured microbial communities within a protective extracellular matrix, shielding fungi from AFs and immune responses [34]. Within biofilms, fungi undergo metabolic and genetic changes, leading to poor drug penetration, altered targets, and heightened efflux pump activity via ABC transporters and MFS proteins [35]. Mature biofilms can be up to 1000-fold more drug-resistant than planktonic cells, necessitating prolonged therapy and contributing to high recurrence rates. Host-pathogen interactions are crucial in the progression and persistence of onychomycosis, independent of biofilm-associated resistance [36]. The avascular nature of nails limits immune cell access, making infections difficult to treat compared to other sites where robust immune responses occur [37]. The innate immune system, especially neutrophils and macrophages, provides primary defense against fungi. However, dermatophytes such as *T. rubrum* evade this via immune-suppressive strategies. Its mannan glycoprotein impairs macrophage activation and T-cell response, aiding fungal persistence [38]. Fungal proteases and reactive oxygen species (ROS) modulators further inhibit host immunity [39]. In diabetics, impaired immunity and poor peripheral circulation enhance fungal colonization, whereas hyperglycemia fosters fungal growth and biofilm formation, increasing AF resistance. In the elderly, slower nail growth and thicker nail plates hinder drug penetration [40]. These multifactorial resistance mechanisms often result in only temporary relief with standard AF therapy. Thus, novel therapeutic approaches are being explored targeting biofilm disruption using enzymatic agents, NPs, or combination therapies [41]. In addition, immune-modulatory interventions, including host-directed therapies to enhance AF immunity, hold promise for managing chronic and treatment-resistant onychomycosis [42].

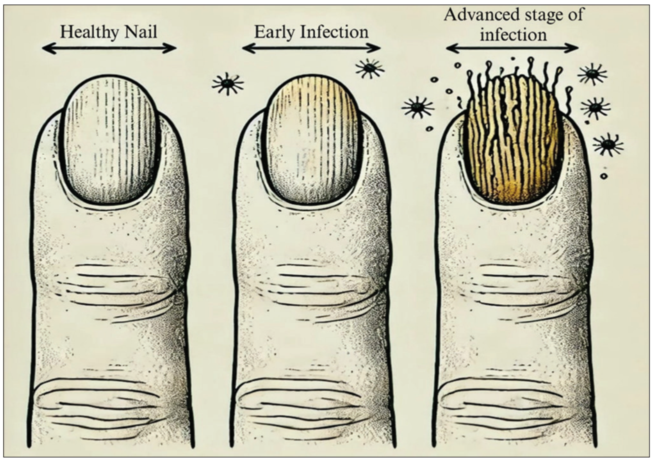

Fig. 1: Different stages of onychomycosis infection

ADVANCES IN AF DRUG DEVELOPMENT

Indeed, treatment of onychomycosis is a difficult task, considering the poor penetration of drugs, frequent relapses, and developing resistance of the fungi. Although systemic AFs, including terbinafine and itraconazole, have been used for a long time, long-term treatment, hepatoxicity, and drug interaction issues highlighted the need for safer and more effective therapy [43]. New developments in AF agents are both systemic and topical and are being discovered with a better combination of efficacy and side effects [44]. The introduction of second-generation azoles and allylamines in systemic therapy and of new topical compounds utilizing benzoxaboroles and penetration enhancers has substantially improved treatment results in superficial infections [45]. These advances are changing the approach to onychomycosis treatment, and bringing hope to those suffering from hard-to-treat or recurrent infections (Fig. 2).

New systemic AF drugs have been developed to address the defects of the previous AFs. Novel azoles such as oteseconazole and isavuconazole provide enhanced selectivity against fungal enzymes with decreased toxicity and increased potency [46]. Oteseconazole, for example, shows higher activity against dermatophytes with less effect against human cytochrome P450 enzymes, reducing the potential for hepatotoxicity and risk of drug interactions [47]. It has a longer duration of half-life that permits less frequent dosing, thereby conferring improved patient compliance. In a similar context, isavuconazole (a broad-spectrum

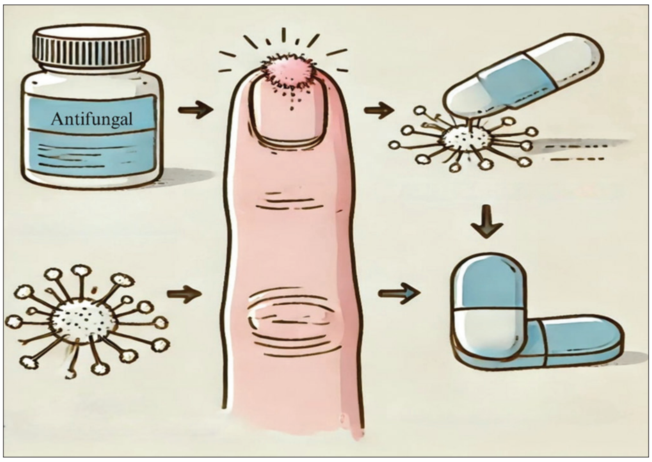

Fig. 2: Various treatment options available for managing onychomycosis

triazole) offers an added advantage of improved bioavailability and tolerability, rendering it ideal for patients intolerant/refractory to conventional azoles [48]. Innovations in allylamines have resulted in terbinafine with increased bioavailability and lipophilicity for better nail bed penetration and shorter treatment courses [49]. In addition, alternative topical AF approaches have been developed for patients who are intolerant of systemic therapy.

Among the benzoxaboroles, tavaborole has shown good nail penetrance and high AF activity [50]. As a therapeutic, tavaborole is unique in that it acts through inhibition of leucyl-tRNA synthetase, a critical enzyme in fungal protein synthesis – as opposed to conventional azoles and allylamines, which ultimately leads to the death of fungal cells. Its low molecular weight can enhance the penetration into the nail matrix with increasing efficacy for persistent infections [51]. By integration of some new drug delivery techniques (such as NP formulations, lipid carriers, and potential penetration-enhancing agents, e.g., urea, dimethyl sulfoxide, etc.), the increment of the penetration of topical formulations to reach the fungi and to destroy them effectively is increasing [52]. Topical combination therapies are also becoming more popular, because they use more than one AF working mechanism to improve the efficacy and minimize the resistance [53]. The combination of azole-allylamine targets several fungal pathways, whereas AF-corticosteroid assists by attenuating inflammation and enhancing drug absorption [54]. Adjuvant therapies, including laser and photodynamic treatment, have also been investigated to improve the penetration of medicaments in the thickened and difficult medicament penetration of nails [55]. The innovation will enable more efficient and patient-friendly therapies to be developed. In the future, research is broadening beyond traditional AF drugs, investigating new therapeutic alternatives, such as peptides AF peptides, RNA-based therapies that silence essential fungal genes, and intelligent delivery systems such as microneedle patches and responsive hydrogels [56]. AF research has been further complemented by artificial intelligence and personalized medicine for the individualization of treatment to the patient profile, thus enhancing cure rates [31]. With the increasing prevalence of drug resistance, these innovations present exciting new options for the treatment of onychomycosis, resulting in more successful and more available treatments with fewer side effects and improved patient outcomes [57].

NANOTECHNOLOGY-BASED AF THERAPIES

Nanotechnology is making tremendous progress in AF therapy by tackling drawbacks possessed by traditional drugs, such as inadequate nail penetration, resistance, and systemic toxicity [30]. The remarkable characteristic features of the NPs, which contribute to enhancing drug delivery, antimycotic effect, and minimizing the side effects, are their dwarf size, high surface area, and functionalization [58]. Based on the entrapment of AFs or the use of the antimicrobial activity of metal NPs, such advanced formulations are trying to overcome more effectively and selectively onychomicosis. NP-encapsulated AFs, as described in Table 1 are one of the most promising areas for the use of nanotechnology in AF therapy is in the use of NP-encapsulated AFs. Traditional AF agents often struggle to penetrate the dense keratin layers of the nail, leading to prolonged treatment durations and high recurrence rates. NP-based drug carriers, such as polymeric NPs, lipid-based NPs, and solid lipid NPs, offer a solution by improving the solubility, stability, and bioavailability of AF agents [59]. For instance, terbinafine or fluconazole encapsulated in NPs can achieve sustained release, ensuring prolonged drug action at the infection site. The nanoscale size enables deeper penetration into the nail bed, improving therapeutic efficacy. Some NPs are even designed with targeted delivery mechanisms, allowing them to release the drug only in the presence of fungal enzymes, reducing off-target effects and minimizing systemic exposure [60]. Liposomal drug delivery systems are another groundbreaking approach that enhances the effectiveness of AF therapy, particularly for topical applications. Liposomes, which are phospholipid vesicles capable of encapsulating hydrophilic and hydrophobic drugs, have demonstrated remarkable improvements in nail penetration [61]. Conventional topical AF creams struggle to reach deep fungal reservoirs within the nail, but liposomal formulations provide better adhesion, controlled drug release, and increased permeability. For instance, the effectiveness of AF liposomal amphotericin B is improved with lower toxicity in comparison with the free drug [62]. New approaches for treating resistant and recurring nail infections are also being investigated, such as hybrid liposomal systems with increased flexibility and penetration properties such as deformable liposomes and ethosomes, which may represent interesting options in the treatment of stubborn nail infections. Nanotechnology and metal NPs with inherent AF properties. Silver, zinc oxide, and copper NPs exhibit a strong AF activity, and this is attributed to its potential of perturbing the fungal cell membrane, inhibiting metabolic pathways, and generating ROS responsible for inducing the oxidative stress in fungal cells [63]. Unlike currently available AF agents acting on specific fungal enzymes or structures, metal NPs have several modes of action, which decreases the possibility of resistance via mutations.

NON-PHARMACOLOGICAL AND NOVEL APPROACHES

Scientists are exploring alternate drug-free and novel ways to treat onychomycosis more effectively since drug resistance and treatment limitations continue to invalidate standard AF therapeutics [73]. When it comes to the alternative treatments strategy offering safer, more targeted, and resistance-free treatment alternatives, including PDT, laser-based treatments, probiotic and microbiome-based therapies, and RNA-based therapeutics, these strategies and a significant amount of promise to change the way onychomycosis is treated using advances in medical technology, microbiology, and genetic engineering shown in Table 2 [74]. PDT and laser treatment represent some of the most exciting recent advances in the treatment of onychomycosis [75].

PDT begins by first treating the infected nail with a photosensitizing substance, after which it is exposed to a certain wavelength of light. ROS that interact in this manner do not damage neighboring tissues, but act against fungal cells only. Compared to conventional AFs, PDT is a site-specific and non-invasive approach that reduces systemic side effects and delinks the potential of drug resistance [76].

Similarly, laser treatments use powerful light to focus and destroy fungal cells through the thermal or photomechanical effect. Exhibiting promising results in enhancing nail appearance and reducing fungal burden, medical devices such as Nd: YAG and diode lasers have been cleared by the Food and Drug Administration for the treatment of onychomycosis [77]. These treatment options are particularly useful in individuals who are unable to take systemic AF therapy or who have multiple infections that do not respond to standard therapy.

Table 1: Nanotechnology-based antifungal therapies for onychomycosis

Technology approach	Nanoparticle type	Drug/formulation	Mechanism of action	Key findings	References
Nanoparticle-encapsulated AFs	Liposomal NPs	Liposomal amphotericin B	Increased penetration into the nail bed, reduced systemic toxicity	Enhanced drug retention and higher AF efficacy	[64]
	Polymeric NPs	PLGA-encapsulated terbinafine	Sustained drug release and increased bioavailability	Improved AF activity and prolonged effect	[65]
	Chitosan NPs	Ciclopirox-loaded chitosan NPs	Mucoadhesive properties allow longer drug retention	Increased AF activity, biofilm inhibition	[66]
Metallic nanoparticles with intrinsic AF properties	Silver (AgNPs)	Silver nanoparticle-based topical gel	Disrupts fungal cell membranes, inhibits biofilms	Strong AF activity with minimal side effects	[67]
	Zinc oxide (ZnO NPs)	ZnO nanoparticle-based nail lacquer	Generates reactive oxygen species to kill fungi	Inhibits fungal growth, enhances penetration	[68]
Liposomal drug delivery for enhanced nail penetration	Liposome-based formulations	Efinaconazole-loaded liposomes	Encapsulates the drug for deeper nail penetration	Increased drug retention and clinical cure rates	[69]
Nanocarrier-based drug delivery	Solid lipid nanoparticles (SLNs)	Terbinafine-SLNs topical gel	Improves solubility and stability, enhances penetration	Better drug absorption and reduced side effects	[70]
Hybrid nanostructures	Metal-polymer hybrids	Terbinafine-silver hybrid nanoparticles	Synergistic AF effect via membrane disruption	Faster nail clearance and superior efficacy	[71]
Nano-emulsions and nano-gels	Nano-emulsion-based drug delivery	Ciclopirox nano-emulsion	Improves drug solubility and skin penetration	Increased AF efficacy compared to conventional formulations	[72]

AFs: Antifungals, NPs: Nanoparticles

Table 2: Clinical studies on emerging antifungal therapies for onychomycosis

Therapy type	Drug/intervention	Study design	Sample size	Key findings	References
Next-generation systemic AFs	Oteseconazole (VT-1161)	Phase II, randomized, double-blind	200+patients	Higher efficacy with fewer side effects than fluconazole	[89]
	Isavuconazole	Phase II, multicenter	150 patients	Effective against resistant dermatophytes; well tolerated	[90]
	Ibrexafungerp (SCY-078)	Phase III, open-label	300 patients	Promising alternative for azole-resistant infections	[91]
Topical innovations	Efinaconazole 10%	Phase III, randomized, controlled	1655 patients	Superior cure rates compared to ciclopirox	[92]
	Tavaborole 5%	Phase III, double-blind	1200+patients	Significant nail penetration and clinical improvement	[93]
	Combination therapy (ciclopirox+terbinafine)	Phase II, randomized	250 patients	Enhanced efficacy over monotherapy	[94]
Nanotechnology-based therapies	Liposomal amphotericin B	Phase II, pilot study	60 patients	Improved penetration and reduced toxicity	[95]
	Silver nanoparticles	Pre-clinical and early clinical	40 patients	Strong AF activity with minimal side effects	[96]
Non-pharmacological approaches	Photodynamic therapy with methylene blue	Phase II, randomized	100 patients	Effective in moderate onychomycosis cases	[97]
	Nd: YAG laser therapy	Phase III, comparative	180 patients	Comparable efficacy to oral terbinafine with fewer risks	[98]
	Probiotic Therapy (*Lactobacillus*-based topical)	Phase I/II, open-label	50 patients	Potential AF activity; further studies needed	[99]
	RNA-based therapeutics (siRNA against fungal genes)	Pre-clinical	N/A	Promising inhibition of fungal growth	[100]

AF: antifungals, siRNA: Small interfering RNA

In addition to light-based therapies, the microbiome and probiotics are taking a prominent place in the treatment of onychomycosis. Frequently precipitated by antibiotics, immunosuppression, or external factors, the disruption of this delicate balance can promote conditions conducive to fungal challenge. Probiotic therapies aim to re-establish this balance through the addition of beneficial bacteria, which compete with fungal pathogens for space and nutrients [78]. Other studies have shown that certain probiotic strains, such as *Lactobacillus* and *Bacillus subtilis*, produce AF compounds that inhibit the growth of dermatophytes. In addition, attempts to modulate the microbiome (with pre- and/or postbiotics) are explored to reinforce the innate defense response within the nail microbiota. Another novel intervention that shows promise is RNA based therapeutics and gene silencing, providing a very specific tool to tackle fungal infections at the genetic level [79]. RNA interference efficiently inhibits fungal growth and survival through the silencing of essential fungal genes using small interfering RNAs. Fungi have a hard time developing resistance to direct genetic manipulation, so that approach is particularly promising as it lowers the likelihood of resistance developing. Researchers are also studying antisense oligonucleotides that can suppress the expression of genes associated with fungal biofilm formation and virulence. These treatments could provide long-lasting answers for onychomycosis by stopping fungi from clinging to the nail bed or creating resistance mechanisms. Advances in *CRISPR-Cas9* gene-editing technology are also creating new opportunities for directly targeting fungal pathogens while maintaining the natural microbiota of the host [37]. The treatment of onychomycosis is undergoing a significant change with the investigation of non-pharmacological and creative AF strategies. Although still in different phases of research and development, these treatments clearly have the possibility to offer safer, more focused, and long-lasting solutions. As laser and PDT technologies become more accessible, microbiome-based interventions advance, and RNA-based therapeutics gain traction, the future of onychomycosis treatment will likely move beyond conventional AFs, offering patients more effective and less invasive options for managing this persistent condition [57].

CLINICAL TRIALS AND FUTURE PERSPECTIVES

Despite the rapid advancements in AF therapy, translating these innovations into effective clinical practice remains a significant challenge. Emerging AF treatments, including next-generation systemic drugs, nanotechnology-based delivery systems, and non-pharmacological therapies, have demonstrated promising results in pre-clinical and early-stage trials [80]. However, several hurdles, including regulatory approvals, cost, long-term safety, and real-world efficacy, must be addressed before these novel therapies become mainstream treatments for onychomycosis [81]. One of the primary concerns in translating innovations to clinical practice is the heterogeneity of onychomycosis cases. The infection varies in severity, causative fungal species, and patient demographics, making it difficult to develop a universal treatment approach. Many emerging therapies, such as RNA-based AFs and microbiome-targeted treatments, have shown strong potential in controlled laboratory environments but lack extensive, large-scale, multi-center clinical trials to validate their efficacy across diverse patient populations [82]. In addition, bioavailability and drug penetration remain key obstacles. The high cost of developing these sophisticated therapies could result in limited access, especially in poorer areas where onychomycosis is usually left untreated because of financial limitations [83].

Regulatory bodies, including the FDA and EMA, want years' worth of thorough safety and efficacy data. Often, this drawn-out schedule leads pharmaceutical companies to give more commercially viable medications priority over niche AF therapies, hence postponing innovation in the sector [84]. Notwithstanding these obstacles, the future of onychomycosis management seems bright. To obtain better therapeutic results, researchers are actively developing improved combination treatments combining several treatment modalities, including NP-based drug delivery with laser therapy or probiotic-based approaches combined with systemic AFs [85]. AI-driven drug discovery is also hastening the discovery of new AF chemicals, therefore enabling the creation of very selective drugs with little adverse effects. As personalized medicine advances, patient-specific treatment strategies based on genetic and microbiome profiling could become a reality, allowing for more precise and effective interventions. Increased awareness and preventative measures will play a key role in reducing the burden of onychomycosis [86].

Future strategies may include vaccination against dermatophyte infections, better hygiene education, and improved screening methods to detect early-stage fungal infections before they become severe. Public health initiatives aimed at promoting foot and nail care, especially among high-risk populations such as diabetics and immunocompromised individuals, could significantly reduce the incidence of onychomycosis-related complications [87]. By addressing the challenges associated with drug resistance, treatment accessibility, and regulatory approvals, the next generation of AF therapies could redefine the standard of care for onychomycosis, offering more effective, safer, and patient-friendly treatment options in the years to come [88].

TREATMENT TRENDS

Systemic AFs

Itraconazole and terbinafine have high cure rates. The rates of mycotic cure were 76% for terbinafine, 63% for itraconazole pulse therapy, 59% for itraconazole continuous therapy, and 48% for fluconazole. However, these therapies are not devoid of potential adverse effects such as hepatotoxicity and drug-drug interactions [101].

Topical treatments

Topical treatments such as efinaconazole have also been shown to be effective (17% cure rates). Efinaconazole is a topical azole AF that resulted in two- to three-fold higher cure rates than the next-best topical treatment, ciclopirox [102].

PDT

This emerging treatment involves applying a photosensitizer to the affected nail and exposing it to light, effectively reducing fungal presence. However, evidence is still preliminary, and more research is needed to establish its efficacy [103].

FUTURE SCOPE

The future scope in the treatment of onychomycosis (fungal nail infection) looks promising, with advancements in both medical research and treatment technologies. Here are some of the key areas where we may see progress in the coming years:

Laser and light therapies

- Laser treatment: Especially with lasers such as the Nd: YAG, laser therapy is drawing interest as a non-invasive substitute for conventional treatments. Without harming neighboring tissue, lasers can penetrate the nail plate and kill fungal cells [104].
- PDT: Being investigated as a treatment for onychomycosis is PDT, which combines light with photosensitizing chemicals. Although still experimental, it shows promise for non-invasive fungal eradication [105].

Nanotechnology

NPs

Nanotechnology could enable more precisely targeted drug delivery systems for the infection, which could allow AF medications to be delivered straight into the nail and surrounding tissues.

Immunotherapy and vaccines

Immunotherapy

Future choices might be new immunotherapy techniques, such as vaccines that activate the body's immune system to combat fungal infections. These vaccinations could offer long-term defense against reinfection.

Gene therapy

- Genetic modification: Future therapies could include gene therapy to alter cells in the nail and surrounding tissues, therefore increasing their resistance to fungal infections.
- Fungal resistance mechanisms: Knowing the genetic composition of fungi and how they develop treatment resistance could help to create medications aimed at those resistance pathways [106].

Improved diagnostic techniques

Molecular diagnostics

Quicker and more precise identification of the fungus causing onychomycosis will be possible with polymerase chain reaction and other molecular methods. Non-invasive imaging: Technologies that allow non-invasive imaging of the nail and underlying tissue to assess the depth and extent of the infection may help doctors monitor the infection more effectively and adjust treatments accordingly [107].

Natural and alternative therapies

Herbal and plant-based treatments

There is ongoing research into the efficacy of natural compounds (such as tea tree oil, oregano oil, or garlic) in treating onychomycosis. These may offer adjunctive treatments or alternatives for patients who prefer natural therapies.

Probiotics

Exploring the role of probiotics in preventing or treating fungal infections may become more prominent as research on the microbiome and its interaction with fungal pathogens advances [93].

CONCLUSION

Emerging AF therapies are transforming onychomycosis treatment by improving efficacy, drug penetration, and patient adherence. New systemic agents, such as advanced azoles and allylamines, offer stronger AF activity with fewer side effects. Topical treatments, including benzoxaboroles and nanotechnology-based formulations, enhance drug delivery. Non-pharmacological approaches such as PDT and RNA therapeutics provide alternative strategies, especially in resistant cases. However, challenges such as drug resistance, limited clinical validation, high costs, and regulatory barriers remain. Future research should focus on combination therapies, AI-driven drug discovery, and personalized medicine to ensure more effective, accessible, and patient-centered care for managing chronic onychomycosis.

ACKNOWLEDGMENT

We would like to express our sincere gratitude to the President of Uttaranchal University, Shri Jitendra Joshi, for his valuable support and guidance.

AUTHORS' CONTRIBUTIONS

All authors equally contributed to conceptualization, literature search, compilation, and writing different parts of the review article.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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